

DATA EVALUATION RECORD

STUDY 1

CHEM 128976

UNICONAZOLE

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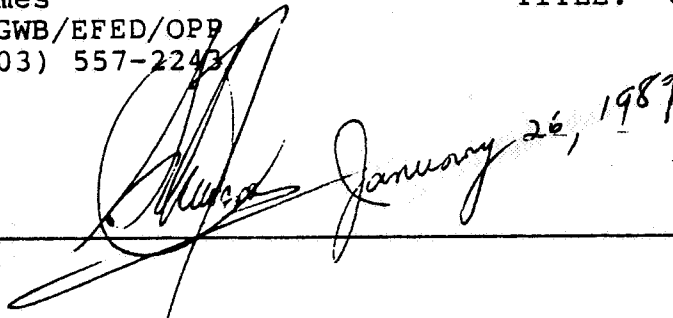
FORMULATION 00 - Radiolabeled Active Ingredient

- a. EPA MRID No. 40345427. Katagi, T., Takahashi, N., Mikami, N., Matsuda, T., and Miyamoto, J. 1986. Hydrolysis of S-3307D in buffer solutions. Performed by Sumitomo Chemical Company, Kyogo, Japan. Laboratory Project Identification IIM-60-0004. Completed December 17, 1986. Submitted by Chevron Chemical Company, Richmond, CA.
- b. EPA MRID No. 40573601. Katagi, T., Takahashi, N., Mikami, N., and Yamada, H. 1988. Reply to EPA's comments on the Report entitled "Hydrolysis of S-3307D in buffer solutions (IIM-60-0004, EPA Accession [MRID] No. 40345427": Part 1. Estimation of Half-life; Part 2. Validation for the Analytical Procedure; Part 3. Reason why hydrolysis study of the other isomers than (S)-E-isomer was not conducted. Performed by Sumitomo Chemical Company, Hyogo, Japan. Laboratory Project Identification IIM60004. Completed March 24, 1988. Submitted by Chevron Chemical Company, Richmond, CA.

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A handwritten signature, possibly reading 'M. S. Termes', is written over a horizontal line. To the right of the signature, the date 'January 26, 1989' is handwritten.

CONCLUSIONS:

In the original hydrolysis study (MRID No. 40345427), several deficiencies were noted. These deficiencies were adequately addressed in the registrant's reply (MRID No. 40573601). Therefore, the hydrolysis study can be considered acceptable to fulfill data requirements for this type of study.

It was shown that at pH 5, 7, and 9, uniconazole did not degrade over a 30-day period. Estimates of half-life values indicate that uniconazole can be persistent for over at least a year. Therefore, hydrolysis is not an important degradation mechanism for uniconazole.

- a. MRID No. 40345427. Katagi, T., Takahashi, N., Mikami, N., Matsuda, T., and Miyamoto, J. 1986. Hydrolysis of S-3307D in buffer solutions. Performed by Sumitomo Chemical Company, Hyogo, Japan. Laboratory Project Identification IIM-60-0004. Completed December 17, 1986. Submitted by Chevron Chemical Company, Richmond, CA.

MATERIALS AND METHODS

Test materials: (S)-(E)-isomer labeled separately in the 4-chlorophenyl (Ph-¹⁴C) and 1,2,4-triazolyl (Trz-¹⁴C) rings. The radiochemical purities were > 99.1% (determined by TLC, autoradiography, and liquid scintillation counting of radioactive areas). The optical purities were > 99% (by HPLC). The specific activities were, ¹⁴Ci/mole (5.68 x 10⁻¹¹ dpm/g) for the [Ph-¹⁴C]-isomer and 49 ¹⁴Ci/mole (3.73 x 10⁻¹¹ dpm/g) for the [Trz-¹⁴C]-isomer.

Buffered solution: The electrical conductivity of the water used to prepare the buffered solutions was 0.062 uS/cm. The buffered solutions consisted of:
pH 5, 0.2M acetic acid/0.2M sodium acetate
pH 7, 0.2M potassium dihydrogen phosphate/0.2M sodium hydroxide
pH 9, 0.2M boric acid + 0.2M potassium chloride/0.2M sodium hydroxide
The pH was adjusted to the desired value at 25°C against a standard buffer solution. Each of the buffer solutions was sterilized at 120°C for 30 min immediately before use.
To prepare the study solutions, the desired ¹⁴C-labeled material was dissolved in chloroform. The chloroform solution was transferred to a heat-sterilized 500 mL Erlenmeyer flask wrapped with aluminum foil and the solvent evaporated under a stream of nitrogen gas. After 300 mL of the desired buffered solution were added, the flasks were closed (stoppered cocks) and mechanically shaken for 2 h. The final concentration of the (S)-(E)-isomer was ca. 0.3 ppm. All the solutions were kept in the incubator at 25±1 °C under dark conditions for 30 days.

Sampling and analytical methods: Solutions were sampled at 0, 5, 10, 20, and 30 days after incubation. To determine the radiocarbon concentration (by LSC), 0.5 mL aliquots were removed from the solutions. Degradation products were analyzed by withdrawing 50 mL aliquots, followed by acidification to pH 1 with 1M HCl, and subsequent extraction with 30 mL of ethyl

acetate (3 times). After measuring the volumes of the aqueous and organic layers, aliquots (1.0 and 0.5 mL, respectively) were taken for radioassaying. Anhydrous sodium sulfate was used to dry the combined organic layer, which was then concentrated to dryness (rotating evaporator/reduced pressure). Two-dimensional TLC was used for analysis (Solvent A, 1st. direction: benzene/acetone, 3/1; Solvent B, 2nd. direction: toluene/ethyl formate/formic acid, 5/7/1).

HPLC (Hitachi 638-50 with a Sumipax® OA-2200 column, a UV-detector, a radioactivity monitor, and hexane/dichloroethane/ethanol as the mobile phase) was used to examine the occurrence of R/S epimerization of the (S)-(E)-isomer. The 30-day sample solutions were extracted with ethyl acetate and analyzed by TLC (Solvent A). The radioactive zones corresponding to the E-isomers were scraped off, eluted with chloroform, and the eluates analyzed by HPLC.

Reported results

Tables I and II present the results for [Ph-¹⁴C]- and [Trz-¹⁴C]-(S)-(E) isomers, respectively. At all times and under the three different pH environments studied, over 98% of the recovered radioactivity was associated with the parent (S)-(E)-isomer. Although some evidence for the presence of trace amounts of the Z-geometrical isomers was seen in the autoradiograms (pH 9; 30 days), there was no tendency for an increase with time. Thus, from the results it is apparent that the parent compound is resistant to hydrolysis at pH 5, 7, and 9 (25 °C, dark, sterile conditions) and that the E/Z isomerization and R/S epimerization did not occur under these conditions.

Reviewer's comments

No attempts were made to provide any half-life estimate for the hydrolysis of the (S)-(E)-isomer. Under the Analysis of the hydrolysis products section (p.4) it is said that for "analysis of the degradation products, 50 mL aliquots were taken and extracted three times with 30 mL of ethyl acetate after acidification to pH 1 with 1M HCl." This, as stated, is a drastic change in pH that may have induced the isomerization/epimerization of any non-(S)-(E)-isomers that may have been present in the buffered solutions back to the parent (S)-(E)-isomer. Do the authors have any evidence that the (R/S)-(Z)- or (R)-(E)-isomers do not isomerize and/or epimerize to the (S)-(E)-isomer under such a drastic pH change?

The hydrolysis study was conducted only with one of the isomers present in the Technical product. Although (S)-(E)-

isomer is the most bioactive one and the predominant isomer in the Technical product, the hydrolysis study should also have included the other three isomers. In the aerobic soil metabolism studies the four isomers were investigated.

Therefore, as presented, the study is not acceptable.

- b. MRID No. 40573601. Katagi, T., Takahash, N., Mikami, N., and Yamada, H. 1988. Reply to EPA's comments on the Report entitled "Hydrolysis of S-3307D in buffer solutions (IIM-60-0004, EPA Accession [MRID] No. 40345427": Part 1 Estimation of Half-life; Part 2. Validation for the Analytical Procedure; Part 3. Reason why hydrolysis study of the other isomers than (S)-E-isomer was not conducted. Performed by Sumitomo Chemical Company, Hyogo, Japan. Laboratory Project Identification IIM60004. Completed March 24, 1988. Submitted by Chevron Chemical Company, Richmond, CA.

The deficiencies noted in the hydrolysis study (MRID No. 40345427) were addressed in this report.

Part 1. Estimation of half-life

An attempt was made to compute half-life values for the hydrolysis of uniconazole by a least-square method. Although the correlation coefficients were low, the data and results indicate that uniconazole is highly persistent. The computed half-life values were, in all cases, greater than one year (Table 1).

Part 2. Validation of the analytical procedure.

In the review of the hydrolysis study (MRID No. 40345427), it was questioned if the rapid acidification to pH 1 followed by extraction with ethyl acetate affected the conversion of any isomers that might have been present back to the parent (S)-(E)-isomer.

Additional experiments submitted by the registrant (in which each of the four possible isomers treated with each of the same buffers used in the hydrolysis study were acidified to pH 1.0 with 1.0 M HCl, extracted with ethyl acetate, and subsequently analyzed by TLC, LSC, and HPLC) showed that the rapid acidification did not result in E/Z isomerization or R/S epimerization. Thus, it can be concluded that the analytical procedure was valid. Results are shown in Tables 2-5.

Part 3. Reason why hydrolysis study of the other than the (S)-E-isomer was not conducted.

The registrant provided experimental evidence that the other isomers (R)-E-; (S)-Z; (R)-Z- and parent (S)-E- did not hydrolyze under rigorous conditions

(1.0 M HCl) or under 0.1 M HCl or NaOH. Results are shown in Table 6-9.

Reviewer's comments

The reviewer accepts the registrant's conclusions as valid. Therefore, the deficiencies noted in the hydrolysis study have been properly addressed and data requirements for hydrolysis studies of uniconazole can be considered fulfilled.